

Colchicine for pericarditis: hype or hope?

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Colchicine has been effectively used in the treatment of several inflammatory conditions, such as gouty attacks, serositis related to familial Mediterranean fever, Behçet syndrome, and more recently also in acute and recurrent pericarditis. Growing evidence has shown that the drug may be useful to treat an acute attack and may be a way to cope with the prevention of pericarditis in acute and recurrent cases and after cardiac surgery. Nevertheless, clinicians are often sceptical about the efficacy of the drug, and concerns have risen on possible side effects and tolerability. In this review, we analyse current evidence to support the use of the drug, as well as possible harms and risks related to drug interactions, reaching the conclusion that colchicine is safe and useful in recurrent pericarditis, if specific precautions are followed, although less evidence supports its use for the treatment of acute pericarditis, where colchicine remains optional and there is a need for further multicentre confirmatory studies. This paper also reviews specific dosing and precautions for the clinical use.

Keywords Colchicine • Pericarditis • Prevention • Therapy

Background

Colchicine is a potentially poisonous natural product and secondary metabolite, originally extracted from plants of the genus *Colchicum* (Autumn crocus, *Colchicum autumnale*, also known as the 'meadow saffron'). Its name comes from Colchis or Kolchis (Greek: Κολχίς, Kolchís), an ancient Georgian state and kingdom, on the eastern shore of the Black Sea, where plants were widespread. The first medical use of the bulbs of the meadow saffron has been reported in the first century AD. Colchicum extracts were first described as a treatment for gout in *De Materia Medica* by Pedanius Dioscorides in the first century AD. Colchicine was first isolated in 1820 by the two French chemists P.S. Pelletier and J. Caventon. Originally used to treat rheumatic complaints and especially gouty attacks, it was also prescribed for its cathartic and emetic effects.

Colchicine may be extracted also from *Gloriosa superba* (Figure 1). All parts of this plant contain colchicine and related alkaloids and are therefore dangerously toxic if ingested, especially the tubers; contact with the stems and leaves can cause skin irritation. However, various preparations of the plant are used in traditional medicines for a variety of complaints in both Africa and India.

Although the well-known and official indication for the treatment and prevention of gouty attacks,¹ colchicine has been studied and prescribed for the treatment and prevention of

other inflammatory conditions (i.e. serositis in familial Mediterranean fever—FMF) (Table 1).² More recently, the use of colchicine has been proposed for the treatment and prevention of pericarditis. Following the successful use of the drug in the treatment and prevention of polyserositis related to the FMF, Bayes de Luna and co-workers proposed the use of the drug for recurrent pericarditis for the first time in 1987.³

Following this initial experience, a number of retrospective studies have been published supporting the use of colchicine in recurrent cases (Table 2).^{4,5–8} The main study limitations of these papers are related either to the retrospective design with the lack of a control group, or to the small sample size. The largest experience is a multicentre retrospective study of 51 patients with recurrences, where only 7 of 51 patients (13.7%) presented with new recurrences during 1004 patient-months of colchicine treatment.⁴ In a recent retrospective multicentre analysis,⁹ where published and unpublished cases treated with colchicine after at least two relapses were aggregated, only 21 of 119 patients (17.6%) presented with new recurrences under colchicine treatment, and 30% after its discontinuation.

On the basis of cumulative anecdotal evidence, observational studies on recurrent pericarditis, and expert consensus, colchicine has been recommended in the treatment of recurrent pericarditis (class I recommendation in the 2004 guidelines of the European Society of Cardiology), and considered optional, but probably

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useful in acute pericarditis (class IIa recommendation in European guidelines).¹⁰ In the guidelines, the recommended dose is 2 mg/day for 1–2 days, followed by a maintenance dose of 1 mg/day. However, several authors recommend that colchicine should be administered to patients with two or more relapses, and thus only after the failure of conventional treatment.^{11,12}

Growing evidence suggests that early use of colchicine may be beneficial. The strongest evidence to support the use of the drug in recurrent pericarditis comes from an open-label clinical trial (CORE), where colchicine, as adjunct to conventional treatment, significantly decreased the subsequent recurrence rate (actuarial rates at 18 months were, respectively, 24.0 vs. 50.6%, $P = 0.022$; NNT = 4.0; 95% CI 2.5–7.1) and symptoms persistence at 72 h (respectively 9.5 vs. 31.0%; $P = 0.029$) in 84 patients with a first recurrence.¹³

Weak evidence has been reported to support the use of colchicine for acute pericarditis (first attack) before 2005. A preliminary small French study without a control group¹⁴ tested the use of

colchicine in 19 patients with a first episode of acute pericarditis. After a mean follow-up of 5 months, a recurrence rate of 10.5% was found. In the recently published open-label clinical trial (COPE), colchicine, as adjunct to conventional treatment, significantly decreased the subsequent recurrence rate (actuarial rates at 18 months were, respectively, 10.7 vs. 32.3%, $P = 0.004$; NNT = 5.0) and symptoms persistence at 72 h (respectively 11.7 vs. 36.7%; $P = 0.003$) in 120 patients with a first episode of acute pericarditis.¹⁵ Colchicine was discontinued in five patients (8.3%) because of diarrhoea.

In both trials (CORE and COPE), which represent the first randomized studies on the management of pericarditis, a maintenance dose of 0.5 mg twice daily was adopted, and reduced to 0.5 mg daily in patients <70 kg, thus lower doses may be equally efficacious but with a possible lower rate of side effects. The available evidence for the recommended duration of treatment in acute (3 months) and recurrent pericarditis (6 months) is based on data from first observational studies in acute and recurrent pericarditis,^{3–8,14} and the more recent COPE and CORE trials.^{13,15} In recurrent more severe cases, some authors advocate a longer use of the drug up to 12–24 months after the last recurrence, tailored to the single patient and with a gradual tapering,^{4,12} considering also that recurrences have been described after colchicine discontinuation.^{9,12}

In pericarditis, a sustained anti-inflammatory effect may be beneficial in autoimmune (autoreactive) forms, but it is still unclear if it may delay the clearance of an infectious agent in other cases. This does not seem the case in the COPE trial, but further evidence is needed before routine use of the drug can be recommended in acute pericarditis.

On the contrary, the drug has been shown not to be efficacious in chronic pericardial effusion and when there is no evidence of inflammation (i.e. cases with negative C-reactive protein).^{4,12,16,17}

Mechanism of action

Three major interactions of colchicine with specific proteins modulate its pharmacokinetics: tubulin, cytochrome P450 3A4 (CYP3A4), and P-glycoprotein. Tubulin is ubiquitous and the main colchicine-binding protein. Cytochrome P450 3A4 is mainly

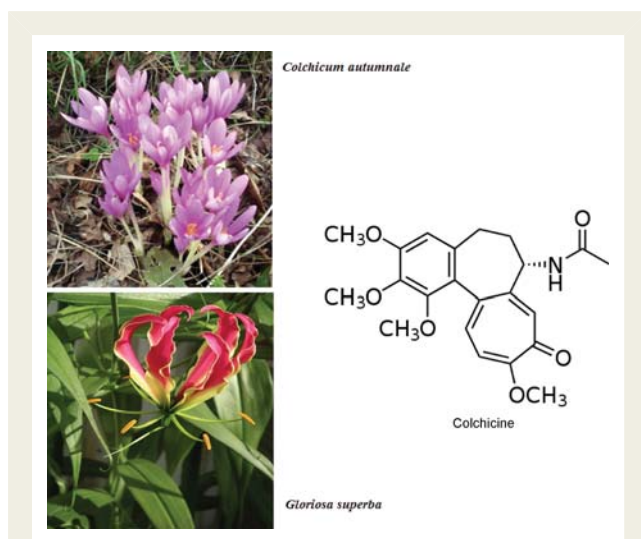


Figure 1 Colchicine can be extracted from two plants of the lily family: *Colchicum autumnale* (meadow saffron) and *Gloriosa superba* (glory lily).

Table 1 More common indications and dosing of colchicine

Indication	Dosing
Gouty arthritis	
Prophylaxis	Oral: 0.5–0.6 mg twice daily
Acute attack	Oral: 0.5–1.2 mg (initial) followed by 0.5–0.6 mg every 1–2 h (maximum dose 3–6 mg)
FMF (unlabelled)	
Prophylaxis	Oral: 1–2 mg daily in divided doses
Primary biliary cirrhosis (unlabelled)	Oral: 0.5–0.6 mg twice daily
Pericarditis (unlabelled)	Oral: 0.5–0.6 mg twice daily

In some European countries, colchicine is available only as 1 mg tablets and a single dose is generally 0.5 or 1.0 mg; for dose adjustments, see Table 3; dosing may be reduced to 0.5–0.6 mg/day in patients at risk of toxicity or intolerant. FMF, familial Mediterranean fever.

Table 2 Main published studies on the treatment of recurrent pericarditis by colchicine

Study	Year	Design	Patients	Maintenance dose (mg/day)	Adjunct to standard therapy	Follow-up (months)	Recurrence rate
Guindo et al. ⁵	1990	NR	9	1.0	Yes	10–54	0/9 (0.0%)
Adler et al. ⁶	1994	NR	8	1.0	Yes	18–34	0/8 (0.0%)
Millaire et al. ⁷	1994	NR	19	1.0	No	32–44	4/19 (21.0%)
Adler et al. ⁴	1998	NR	51	1.0	Yes	6–128	7/51 (13.7%)
Imazio et al. ⁸	2005	NR	35	1.0	Yes	48–108	3/35 (8.6%)
CORE ¹³	2005	R	84	0.5–1.0	Yes	8–44	9/42 (21.0%)

Recurrence rate in patients treated with colchicine.
Year, publication year; NR, not randomized, observational; R, randomized trial.

Table 3 Colchicine dose adjustment according to age and renal or hepatic dysfunction

Condition	Dose adjustment
Children	
≤5 years	0.5 mg/day
>5 years	1.0–1.5 mg/day in two to three divided doses
Elderly (>70 years)	Reduce dose by 50%
Renal impairment	
Cl _{cr} 35–49 mL/min	0.5–0.6 mg once daily
Cl _{cr} 10–34 mL/min	0.5–0.6 mg every 2–3 days
Cl _{cr} <10 mL/min	Avoid chronic use of colchicine. Use in serious renal impairment is contraindicated by the manufacturer
Hepatic dysfunction	Avoid in severe hepatobiliary dysfunction and in patients with hepatic disease

found in the intestine and liver, and it is involved in the metabolism of many drugs. Cytochrome P450 3A4 metabolizes colchicine in the liver. P-glycoprotein is an ATP-dependent phosphoglycoprotein located in the cell membrane and responsible for the excretion of the drug in the intestine, liver, kidney, and blood–brain barrier (Figure 2). Different expression and activity of CYP3A4 and P-glycoprotein may be responsible for the wide interindividual response to the drug. Both proteins are also substrate for different drugs, with possible pharmacological interactions that may affect colchicine pharmacokinetics.¹⁸

The onset of the action of colchicine when orally administered is relatively rapid with pain relief achievable within 12–24 h if adequately dosed. Colchicine is promptly absorbed by the jejunum and ileum with a considerable interindividual variability. Although the drug is lipophilic, colchicine is partly blocked by the intestinal barrier with a mean bioavailability of 45% (24–88%) in healthy subjects.¹⁹ This variable bioavailability may explain potential different interindividual responses to the same dose of the drug according to different enterocyte CYP3A4-metabolism and P-glycoprotein excretion. Peak serum concentration is reached within 0.5–2 h after oral administration, then concentration declines for the next 2 h before increasing again owing to enterohepatic recycling. Thus, administration twice daily is able to reach better clinical results, also improving drug tolerability. The drug is able to concentrate in leucocytes, where it exerts marked effects, altering

adhesion, mobility, and cytokine production. These actions explain most of the inflammatory effects of colchicine, giving rise to several therapeutic uses. However, the accumulation in leucocytes is slow with a peak intracellular concentration after 48 h from a 1 mg oral dose in healthy subjects. The biological effects require 24–48 h to develop, and, when the drug is discontinued, colchicine declines with an elimination half-life of 16 h. Thus, biological effects decline after 24–48 h in white blood cells.²⁰

The protein binding is between 10 and 31%. The drug is partially metabolized in the liver by de-acetylation with a half-life elimination of 12–30 min, which is prolonged to 45 min in end-stage renal disease. Colchicine and its metabolites are eliminated by the kidneys and bile. Decreased clearance through either of these two pathways increases the risk of side effects and poisoning. However, the kidneys contribute only 10–20% of colchicine clearance, and hepatic clearance is the main determinant of colchicine accumulation.^{2,21,22} Although colchicine may enter all tissues in the body, P-glycoprotein expression limits the cellular exposition to colchicine in several physiological barriers (i.e. placenta, blood–brain barrier). Nevertheless, P-glycoprotein saturation by other drugs may increase the levels of colchicine, impairing its excretion. Also, colchicine enters breast milk.^{2,23,24}

The exact mechanism of colchicine action is not fully understood. Most of the pharmacological effects of colchicine on cells involved in inflammation appear to be related to the capacity of

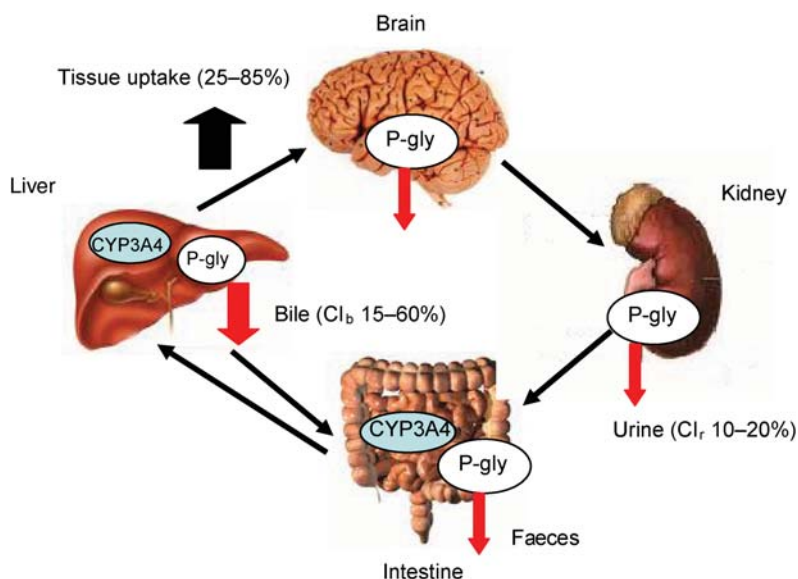


Figure 2 Role of cytochrome P450 3A4 and P-glycoprotein in metabolism and transport of colchicine (see text for details). Cl_b, biliary clearance; Cl_r, renal clearance; P-Gly, P-glycoprotein.

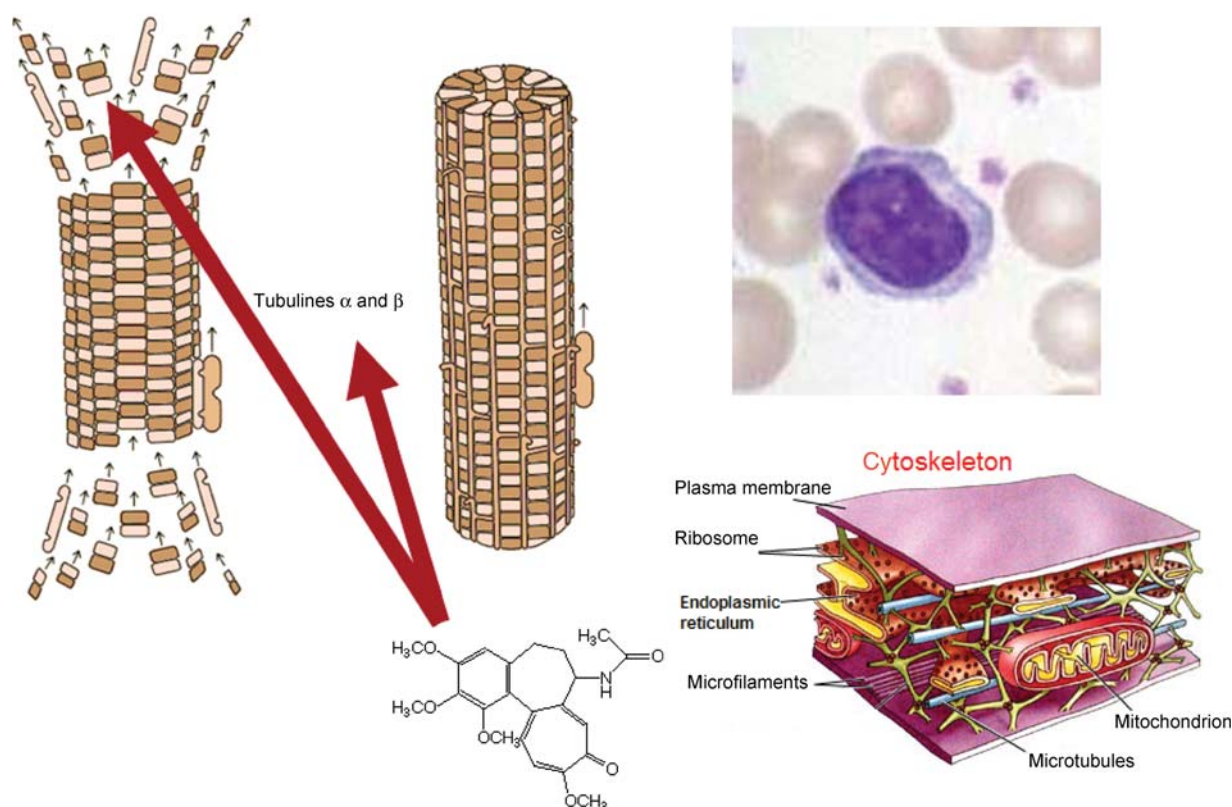


Figure 3 Anti-inflammatory mechanism of colchicine (see text for details).

colchicine to inhibit the process of microtubule self-assembly by binding β -tubulin with the formation of tubulin–colchicine complexes, thus interfering with several cellular functions (such as

chemotaxis, degranulation, phagocytosis) (Figure 3).^{2,4,23,24} On this basis, colchicine decreases leucocyte motility and phagocytosis, thereby reducing the inflammatory response. Colchicine

shows a preferential concentration in leucocytes, and the peak concentration of colchicine may be more than 16 times the peak concentration in plasma.⁴ This effect seems to explain therapeutic effects at low oral doses.^{13,15}

Safety and side effects

At doses of 1–2 mg per day, colchicine is safe even when given continuously over decades.^{25,26} Available data on the dose-dependency of colchicine effects come from cases with acute poisoning. Ingested doses <0.5 mg/kg cause gastrointestinal symptoms and clotting factors deficits. Doses ranging from 0.5 to 0.8 mg/kg induce bone marrow failure and carry a 10% mortality. Death follows ingestion of >0.8 mg/kg. Therapeutic doses range from 0.015 to 0.030 mg/kg with a small therapeutic margin. The narrow therapeutic margin is a source of concern for the physician, but careful dosing may ensure safe use of the drug.

Colchicine therapeutic effects are related to leucocytes concentration of the drug rather than plasma levels; nevertheless, plasma levels may be useful to detect low intestinal absorption, risk of toxicity, and poor compliance. Although there are no available studies that precisely established the therapeutic plasma levels of colchicine, plasma levels between 0.5 and 3 ng/mL correspond to clinical therapeutic effects. Assays should be done at least 8 h after the last dose and are best when performed immediately before the next dose. Wide interindividual colchicine bioavailability may explain different individual susceptibility to the effects of the drug. Lower plasma levels have been detected in non-responders in patients with FMF. Individual differences in colchicine plasma levels may reflect differences in the intestinal absorption, which is dependent on different expression of P-glycoprotein and CYP3A4.

Serious safety concerns have been associated with intravenous colchicine use; 50 reports of serious adverse events have been reported, including 23 deaths (through June 2007).²⁷ Three of these deaths were associated with the use of an improperly compounded intravenous colchicine used to treat chronic back pain—not an accepted practice. In February 2008, the FDA ordered companies to stop manufacturing injectable colchicine within 30 days and to stop shipping the product within 180 days. After these dates, all injectable colchicine products must have FDA approval in order to be manufactured or shipped. Injectable colchicine has a narrow therapeutic index and most related toxicities are dose-related. Recently (October 2007), the only manufacturer of injectable colchicine voluntarily discontinued production. The FDA also strongly discourages the compounding of injectable colchicine owing to serious safety risks. Oral colchicine tablets are not affected by this action. At present, only oral use is recommended, although there are no data on other route of administration (i.e. intrapericardial), and on the possibility to detect colchicine in pericardial tissue or fluid.

Usual side effects are gastrointestinal (up to 10–15% of cases) including nausea, vomiting, diarrhoea, abdominal pain, usually limiting drug compliance and being a common cause of drug withdrawal^{2,4,13,15}; although generally mild, they may resolve with dose reduction. Weight-adjusted doses, such as in the COPE and CORE trials, may halve these side effects.^{13,15} Other common side effects at higher doses include other gastrointestinal side effects with anorexia, elevation of transaminases, and alopecia

(1–10%). In <1% of cases, other side effects are reported, including agranulocytosis, aplastic anaemia, bone marrow suppression, hepatotoxicity, and myotoxicity.^{2,4,15,23,24}

Colchicine inhibition of cell division has raised concern about the possible adverse effects in patients treated prior to conception, during pregnancy or breast-feeding, or during childhood. Although azoospermia has been reported as a rare possible side effect (<1%), no interference of colchicine treatment was recorded in either growth rate or fertility after a cumulative 15 000 years of follow-up in patients with FMF.^{25,26} In these patients, even prolonged exposure to colchicine seems to have no effects on male or female fertility, pregnancy outcomes, foetal development or development after birth.²⁸

However, in a general population, contraindications include hypersensitivity to colchicine or any component of the formulation, severe renal, gastrointestinal, hepatic, or cardiac disorders, blood dyscrasias, pregnancy.^{13,15}

Dose reduction should be considered in patients who develop gastrointestinal symptoms (anorexia, diarrhoea, nausea, vomiting) or weakness related to drug therapy. Dose adjustment is necessary also for patients with renal impairment, debilitated patients, and the elderly (Table 3). Moreover, monitoring is recommended during therapy with colchicine (blood cell count, transaminase, CK, and renal function test at least at baseline, and after 1 month of treatment).

During oral administration of colchicine, the drug may induce reduced absorption of vitamin B₁₂ and rarely may result in macrocytic anaemia or neurological dysfunction. Supplement with vitamin B₁₂ may be considered in special patients subsets.²³

Drug interactions

Colchicine undergoes intensive hepatic metabolism (CYP 3A4). Consequently, drugs that interact with the cytochrome P-450 system may interfere with colchicine, increasing the levels/effects of colchicine (Table 4). CYP3A4 inhibitors (azole antifungals,

Table 4 Major drug interaction with colchicine

Drug	Type	Remedy
Cyclosporine	Reciprocal enhancement of adverse/toxic effects	Consider therapy modification
CYP3A4 inhibitors	May increase levels/effects of colchicine	Monitor therapy
HMG-CoA reductase inhibitors	Increased risk of myotoxicity	Consider therapy modification
Macrolide antibiotics	Decrease colchicine metabolism	Consider therapy modification
Verapamil	Increase verapamil serum concentration, enhance colchicine nephrotoxicity	Monitor therapy

A patient-specific assessment must be conducted to determine whether the benefits of concomitant therapy outweigh the risks. Specific actions must be taken in order to realize the benefits and/or minimize the toxicity resulting from concomitant use of the agents. These actions may include aggressive monitoring, empiric dosage changes, choosing alternative agents.

diclofenac, doxycycline, imatinib, isoniazid, nefazodone, nicardipine, propofol, protease inhibitors, quinidine, telithromycin, and verapamil) may increase toxicity of colchicine.²⁹ Cyclosporine may also increase toxicity of colchicine. On the other hand, colchicine may increase the serum concentration of cyclosporine. Nephrotoxicity, hepatotoxicity, and the risk of myopathies may also be increased.^{30–32}

As mentioned, colchicine is also a substrate of P-glycoprotein, a transporter involved in the elimination of several drugs. Macrolides are inhibitors of P-glycoprotein and cytochrome P450-dependent enzymes and may decrease colchicine excretion. Co-administration of colchicine and macrolides may impair colchicine elimination, resulting in possible drug excess and toxicity particularly in the elderly and/or with renal impairment.^{33–35} At present, it seems reasonable to avoid the co-administration of colchicine and macrolides, as well as the use of the drug in patients with hepatobiliary dysfunction, severe renal, gastrointestinal disorders, and blood dyscrasias. It is also prudent to reduce maintenance/prophylactic dose by 50% in individuals >70 years and in patients with impaired renal function with glomerular filtration rates <50 mL/min (Table 3). Caution is recommended in the use of colchicine in patients with hepatobiliary dysfunction since biliary excretion is the main route of colchicine elimination; the risk of colchicine poisoning is increased in patients with liver diseases such as primary biliary cirrhosis or other forms of cirrhosis.^{21,22} On the other hand, in a cohort of 58 patients with pericarditis,¹² 5 patients (8.6%) presented with abnormal liver tests in the first attack. However, these abnormalities were related to the viral infection and disappeared with the resolution of the attacks. So, this potentially useful therapy may be considered in patients with abnormalities in liver tests caused by the systemic disease itself.²⁹ Dose adjustment may be considered using halved doses in mild-to-moderate liver dysfunction. Severe liver dysfunction is usually considered a contraindication.

An additional interaction is that with HMG-CoA reductase inhibitors (statins). Colchicine may enhance the myopathic (rhabdomyolysis) effect of HMG-CoA reductase inhibitors. Also, it may increase the serum concentration of HMG-CoA reductase inhibitors. At least 9 case reports describe patients in whom myotoxicity, ranging from weakness and myopathy to fatal rhabdomyolysis, developed following the initiation of combination therapy involving colchicine and an HMG-CoA reductase inhibitor (statin).^{36–44} Reported cases have involved simvastatin,^{36–39}

atorvastatin,^{40,41} fluvastatin,⁴² lovastatin,⁴³ and pravastatin.⁴⁴ Although no clear underlying patient risk factors (other than the colchicine–statin association) were present in all cases, several of the patients had at least mildly impaired renal function,^{36,38–40,44} and two were transplant recipients receiving other potentially interacting drugs (i.e. cyclosporine).^{37,41} In most of the cases, muscle weakness was the initial symptom, and the initial onset of symptoms was 2–3 weeks (but as long as several months) after the initiation of the combination. The precise mechanism of this interaction is unclear, but it may have pharmacodynamic and/or pharmacokinetic components. Colchicine and statins have each been independently associated with myotoxicity; in one review of 475 patients hospitalized for rhabdomyolysis, statins and colchicine were among the prescription agents most commonly involved.⁴⁵ In addition, colchicine and many of the statins (lovastatin, simvastatin, atorvastatin) are metabolized to a substantial degree by CYP3A4,⁴⁶ with some *in vitro* evidence suggesting colchicine may inhibit CYP3A4 to some degree.⁴⁷ These data suggest that at least for some statins, colchicine could increase statin concentrations, further increasing the risk of myotoxicity. Further, colchicine may impair the excretion of some statins via the inhibition of organic anion transport, an effect that has been demonstrated *in vitro* with pravastatin.⁴⁸ This action would also lead to increased statin concentrations and increased risk of toxicity.

Thus, it is recommended to carefully monitor for signs of muscle pain and/or weakness with concomitant therapy. Although this is advised with monotherapy involving either agent (since each can independently cause muscle toxicity), it is especially prudent when using in combination. On this basis, every patient should undergo a careful monitoring of possible side effects also including blood analyses (at least transaminases, serum creatinine, CK, and blood cell count) before starting the drug, and later at least after 1 month of treatment.

Future research and ongoing clinical trials

At present, double-blind randomized trials are lacking to guide the evaluation and management of pericarditis, and strategies to prevent recurrences require further investigations.

Results from prospective, randomized, open-label studies suggest that colchicine, as adjunct to conventional therapy, might be a first-line

Table 5 Ongoing multicentre, double-blind randomized trials on the use of colchicine in the treatment and prevention of pericarditis

Trial	Patients to enrol	Treatment arms	Primary endpoint
COPPS ⁴⁹	360 patients after cardiac surgery	Placebo vs. colchicine (primary prevention of PPS)	PPS at 12 months
ICAP ⁵⁰	240 patients with acute pericarditis	Conventional treatment plus placebo vs. conventional treatment plus colchicine	Recurrence rate at 18 months
CORP ⁵¹	120 patients with first recurrence	Conventional treatment plus placebo vs. conventional treatment plus colchicine	Recurrence rate at 18 months
CORP 2 ⁵¹	240 patients with the second or subsequent recurrence	Conventional treatment plus placebo vs. conventional treatment plus colchicine	Recurrence rate at 18 months

COPPS, Colchicine for the Prevention of the PostPericardiotomy Syndrome; ICAP, Investigation on Colchicine in Acute Pericarditis; CORP, Colchicine for Recurrent Pericarditis.

Table 6 Therapeutic schemes with colchicine in pericardial diseases (see text for details)

Disease	Attack dose	Adjunct to	Maintenance	Treatment length
Acute pericarditis	Not necessary (1.0 mg twice daily) ^a	Aspirin, NSAID, or corticosteroids	0.5 mg twice daily ^a	3 months
Recurrent pericarditis	Not necessary (0.5 mg twice daily) ^a	Aspirin, NSAID, or corticosteroids	0.5 mg twice daily ^a	6–12 months

^aFor patients >70 kg; for others, consider halved doses: 0.5 mg twice daily as attack dose and 0.5 mg once daily for maintenance.

drug either in the treatment of acute pericarditis or in recurrent pericarditis. However, further studies are required to validate the use of colchicine for pericarditis. Ongoing multicentre, double-blind randomized trials (Table 5) will provide a stronger evidence-base for or against the routine use of colchicine in pericarditis.^{49–51}

Increasing data have expanded our knowledge on colchicine pharmacology, and now, pharmacogenomic considerations may explain interindividual variability in the response to the drug. It is well known that 5–10% of patients with FMF do not respond to colchicine. Different polymorphisms of P-glycoprotein may explain some of these cases of colchicine resistance.^{52,53} In the future, a better understanding and characterization of these polymorphisms may aid also in the identification of responders and non-responders also in cases of pericarditis not associated to FMF.

Conclusions

Although clinicians are often sceptical on the possible use of colchicine in pericarditis, growing evidence suggests that the drug may be useful in patients with recurrent pericarditis. Common reasons of scepticism include finding of further recurrences on treatment, colchicine failure as monotherapy (efficacy demonstrated almost exclusively for combination therapy with a non-steroidal anti-inflammatory drug—NSAID or corticosteroids), and the need for drug withdrawal owing to gastrointestinal intolerance. Nevertheless, colchicine may halve recurrence when used as adjunct to aspirin, an NSAID or corticosteroids, as in the CORE trial; thus, patients on colchicine may still have recurrences, but they are generally less intense and longer with an improved quality of life and a reduced overall burden of the disease. Practical tips to improve drug compliance may be using appropriate weight-adjusted doses and starting from lower doses without a loading dose, then increasing the dose if tolerated (Table 6).

The choice of treatments for pericarditis should take into account the prognosis, favouring fewer toxic and less expensive drugs,^{11,12,54–56} especially in recurrent cases, where new treatments are often searched. Compared with other drug treatments, colchicine appears to be one of the cheapest (daily cost of \$0.23 in the USA, and €0.13 in western Europe) and safer available treatment if a careful selection and monitoring of patients is followed. The natural history of the disease is characterized by a very active initial phase followed by a late dormant phase with less and less recurrences till a stable remission after an unpredictable time.^{12,56} Drug treatment (above all colchicine) may hasten the progression towards the late

dormant phase, reducing recurrence rate and, thus, improving the quality of life.

Conflict of interest: none declared.

References

- Emmerson BT. The management of gout. *N Engl J Med* 1996;**334**:445–451.
- Lange U, Schumann C, Schmidt KL. Current aspects of colchicine therapy. Classical indications and new therapeutic uses. *Eur J Med Res* 2001;**6**:150–160.
- Rodriguez de la Serna A, Guido J, Marti V, Bayes de Luna A. Colchicine for recurrent pericarditis. (Letter). *Lancet* 1987;**2**:1517.
- Adler Y, Finkelstein Y, Guindo J, Rodriguez de la Serna A, Shoenfeld Y, Bayes-Genis A, Sagie A, Bayes de Luna A, Spodick DH. Colchicine treatment for recurrent pericarditis. A decade of experience. *Circulation* 1998;**97**:2183–2185.
- Guindo J, Rodriguez de la Serna A, Ramio J, de Miguel Diaz MA, Subirana MT, Perez Ayuso MJ, Cosin J, Bayes de Luna A. Recurrent pericarditis: relief with colchicine. *Circulation* 1990;**82**:1117–1120.
- Adler Y, Zandman-Goddard G, Ravid M, Avidan B, Zemer D, Ehrenfeld M, Shemesh J, Tomer Y, Shoenfeld Y. Usefulness of colchicine in preventing recurrences of pericarditis. *Am J Cardiol* 1994;**73**:916–917.
- Millaire A, de Groote P, Decoux E, Goullard L, Ducloux G. Treatment of recurrent pericarditis with colchicine. *Eur Heart J* 1994;**15**:120–124.
- Imazio M, Demicheli B, Parrini I, Cecchi E, Demarie D, Ghisio A, Belli R, Bobbio M, Trinchero R. Management, risk factors, and outcomes in recurrent pericarditis. *Am J Cardiol* 2005;**96**:736–739.
- Artom G, Koren-Morag N, Spodick DH, Brucato A, Guindo J, Bayes-de-Luna A, Brambilla G, Finkelstein Y, Granel B, Bayes-Genis A, Schwammenthal E, Adler Y. Pretreatment with corticosteroids attenuates the efficacy of colchicine in preventing recurrent pericarditis: a multi-centre all-case analysis. *Eur Heart J* 2005;**26**:723–727.
- Maisch B, Seferovic PM, Ristic AD, Erbel R, Rienmuller R, Adler Y, Tomkowski WZ, Thiene G, Yacoub MH, Task Force on the diagnosis management of pericardial diseases of the European Society of Cardiology Guidelines on the diagnosis and management of pericardial diseases. *Eur Heart J* 2004;**25**:587–610.
- Soler-Soler J, Sagrista-Sauleda J, Permanyer-Miralda G. Relapsing pericarditis. *Heart* 2004;**90**:1364–1368.
- Brucato A, Brambilla G, Adler Y, Spodick DH, Canesi B. Therapy for recurrent acute pericarditis: a rheumatological solution? *Clin Exp Rheumatol* 2006;**24**:45–50.
- Imazio M, Bobbio M, Cecchi E, Demarie D, Pomari F, Moratti M, Ghisio A, Belli R, Trinchero R. Colchicine as first-choice therapy for recurrent pericarditis: results of the CORE (Colchicine for REcurrent pericarditis) trial. *Arch Intern Med* 2005;**165**:1987–1991.
- Millaire A, Ducloux G. Treatment of acute or recurrent pericarditis with colchicine. (Letter). *Circulation* 1991;**83**:1458–1459.
- Imazio M, Bobbio M, Cecchi E, Demarie D, Demicheli B, Pomari F, Moratti M, Gaschino G, Giammaria M, Ghisio A, Belli R, Trinchero R. Colchicine in addition to conventional therapy for acute pericarditis: results of the COLchicine for acute PERicarditis (COPE) trial. *Circulation* 2005;**112**:2012–2016.
- Adler Y, Guindo J, Finkelstein Y, Khouri A, Assali A, Bayes-Genis A, Bayes de Luna A. Colchicine for large pericardial effusion. *Clin Cardiol* 1998;**21**:143–144.
- Brucato A, Brambilla G, Adler Y, Spodick DH. Colchicine for recurrent acute pericarditis. *Arch Intern Med* 2006;**166**:696.
- Niel E, Scherrmann JM. Colchicine today. *Joint Bone Spine* 2006;**73**:672–678.
- Rochdi M, Sabouraud A, Girre C, Venet R, Scherrmann JM. Pharmacokinetics and absolute bioavailability of colchicine after i.v. and oral administration in healthy human volunteers and elderly subjects. *Eur J Clin Pharmacol* 1994;**46**:351–354.
- Fordham JN, Kirwan J, Cason J, Currey HL. Prolonged reduction in polymorphonuclear adhesion following oral colchicine. *Ann Rheum Dis* 1981;**40**:605–608.

21. Rudi J, Raedsch R, Gerteis C, Schlenker T, Plachky J, Walter-Sack I, Sabouraud A, Scherrmann JM, Kommerell B. Plasma kinetics and biliary excretion of colchicine in patients with chronic liver disease after oral administration of a single dose and after long-term treatment. *Scand J Gastroenterol* 1994;**29**:346–351.
22. Leighton JA, Bay MK, Maldonado AL, Schenker S, Speeg KV. Colchicine clearance is impaired in alcoholic cirrhosis. *Hepatology* 1991;**14**:1013–1015.
23. Levy M, Spino M, Read SE. Colchicine: a state-of-the-art review. *Pharmacotherapy* 1991;**11**:196.
24. Molad Y. Update on colchicine and its mechanism of action. *Curr Rheumatol Rep* 2002;**3**:252–256.
25. Ben-Chetrit E, Levy M. Colchicine prophylaxis in familial Mediterranean fever: reappraisal after 15 years. *Semin Arthritis Rheum* 1991;**20**:241–246.
26. Zemer D, Livneh A, Danon YL, Pras M, Sohar E. Long term colchicine treatment in children with familial Mediterranean fever. *Arthritis Rheum* 1991;**34**:973–977.
27. Centers for Disease Control and Prevention (CDC). Deaths from intravenous colchicine resulting from a compounding pharmacy error—Oregon and Washington, 2007. *MMWR Morb Mortal Wkly Rep* 2007;**56**:1050–1052.
28. Ben-Chetrit E, Levy M. Reproductive system in familial Mediterranean fever: an overview. *Ann Rheum Dis* 2003;**62**:916–919.
29. Brucato A, Adler Y, Spodick DH. Letter regarding article by Imazio et al. Colchicine in addition to conventional therapy for acute pericarditis. *Circulation* 2006;**113**:e693. [Author reply e693–e694].
30. Menta R, Rossi E, Guariglia A, David S, Cambi V. Reversible acute cyclosporine nephrotoxicity induced by colchicine administration. *Nephrol Dial Transplant* 1987;**2**:380–381.
31. Rieger EH, Halasz NA, Wahlstrom HE. Colchicine neuromyopathy after renal transplantation. *Transplantation* 1990;**49**:1196–1198.
32. Rumpf KW, Henning HV. Is myopathy in renal transplant patients induced by cyclosporine or colchicine? *Lancet* 1990;**335**:800–801.
33. Rollet F, Pajot O, Chauvelot-Moachon L, Nazal EM, Kélaïdi C, Blanche P. Acute colchicine intoxication during clarithromycin administration. *Ann Pharmacother* 2004;**38**:2074–2077.
34. Cheng VC, Ho PL, Yuen KY. Two probable cases of serious drug interaction between clarithromycin and colchicines. *South Med J* 2005;**98**:811–813.
35. Hung IF, Wu AK, Cheng VC, Tang BS, To KW, Yeung CK, Woo PC, Lau SK, Cheung BM, Yuen KY. Fatal interaction between clarithromycin and colchicine in patients with renal insufficiency: a retrospective study. *Clin Infect Dis* 2005;**41**:291–300.
36. Justiniano M, Dold S, Espinoza LR. Rapid onset of muscle weakness (rhabdomyolysis) associated with the combined use of simvastatin and colchicine. *J Clin Rheumatol* 2007;**13**:266–268.
37. Francis L, Bonilla E, Soforo E, Neupane H, Nakhla H, Fuller C, Perl A. Fatal toxic myopathy attributed to propofol, methylprednisolone, and cyclosporine after prior exposure to colchicine and simvastatin. *Clin Rheumatol* 2008;**27**:129–131.
38. Baker SK, Goodwin S, Sur M, Tarnopolsky MA. Cytoskeletal myotoxicity from simvastatin and colchicine. *Muscle Nerve* 2004;**30**:799–802.
39. Hsu WC, Chen WH, Chang MT, Chiu HC. Colchicine-induced acute myopathy in a patient with concomitant use of simvastatin. *Clin Neuropharmacol* 2002;**25**:266–268.
40. Tufan A, Dede DS, Cavus S, Altintas ND, Iskit AB, Topeli A. Rhabdomyolysis in a patient treated with colchicine and atorvastatin. *Ann Pharmacother* 2006;**40**:1466–1469.
41. Phanish MK, Krishnamurthy S, Bloodworth LL. Colchicine-induced rhabdomyolysis. *Am J Med* 2003;**114**:166–167.
42. Atasoyu EM, Evrenkaya TR, Solmazgul E. Possible colchicine rhabdomyolysis in a fluvastatin-treated patient. *Ann Pharmacother* 2005;**39**:1368–1369.
43. Torgovnick J, Sethi N, Arsura E. Colchicine and HMG Co-A reductase inhibitor induced myopathy—a case report. *Neurotoxicology* 2006;**27**:1126–1127.
44. Alayli G, Cengiz K, Cantürk F, Durmuş D, Akyol Y, Menekşe EB. Acute myopathy in a patient with concomitant use of pravastatin and colchicine. *Ann Pharmacother* 2005;**39**:1358–1361.
45. Melli G, Chaudhry V, Cornblath DR. Rhabdomyolysis: an evaluation of 475 hospitalized patients. *Medicine (Baltimore)* 2005;**84**:377–385.
46. Tateishi T, Soucek P, Caraco Y, Guengerich FP, Wood AJ. Colchicine biotransformation by human liver microsomes. Identification of CYP3A4 as the major isoform responsible for colchicine demethylation. *Biochem Pharmacol* 1997;**53**:111–116.
47. Dvorak Z, Modriansky M, Pichard-Garcia L, Balaguer P, Vilareim MJ, Ulrichová J, Maurel P, Pascussi JM. Colchicine down-regulates cytochrome P450 2B6, 2C8, 2C9, and 3A4 in human hepatocytes by affecting their glucocorticoid receptor-mediated regulation. *Mol Pharmacol* 2003;**64**:160–169.
48. Takikawa H, Sano N, Akimoto K, Ogasawara T, Yamanaka M. Effects of colchicine and phenothiazine on biliary excretion of organic anions in rats. *J Gastroenterol Hepatol* 1998;**13**:427–432.
49. Imazio M, Cecchi E, Demicheli B, Chinaglia A, Coda L, Ghisio A, Demarie D, Ierna S, Trinchero R, COPPS Investigators. Rationale and design of the COPPS trial: a randomised, placebo-controlled, multicentre study on the use of colchicine for the primary prevention of postpericardiotomy syndrome. *J Cardiovasc Med* 2007;**8**:1044–1048.
50. Imazio M, Cecchi E, Ierna S, Trinchero R, on behalf of the ICAP Investigators. Investigation on colchicine for acute pericarditis: a multicenter randomized placebo-controlled trial evaluating the clinical benefits of colchicine as adjunct to conventional therapy in the treatment and prevention of pericarditis; study design and rationale. *J Cardiovasc Med* 2007;**8**:613–617.
51. Imazio M, Cecchi E, Ierna S, Trinchero R, on behalf of the CORP Investigators-CORP (Colchicine for Recurrent Pericarditis) and CORP-2 trials: two randomized placebo-controlled trials evaluating the clinical benefits of colchicine as adjunct to conventional therapy in the treatment and prevention of recurrent pericarditis. Study design and rationale. *J Cardiovasc Med* 2007;**8**:830–834.
52. Lidar M, Kedem R, Langevitz P, Pras M, Livneh A. Intravenous colchicine for treatment of patients with familial Mediterranean fever unresponsive to oral colchicine. *J Rheumatol* 2003;**30**:2620–2623.
53. Tufan A, Babaoglu MO, Akdogan A, Yasar U, Calguneri M, Kalyoncu U, Karadag O, Hayran M, Ertenli AI, Bozkurt A, Kiraz S. Association of drug transporter gene ABCB1 (MDR1) 3435C to T polymorphism with colchicine response in familial Mediterranean fever. *J Rheumatol* 2007;**34**:1540–1544.
54. Imazio M, Trinchero R, Shabetai R. Pathogenesis, management, and prevention of recurrent pericarditis. *J Cardiovasc Med* 2007;**8**:404–410.
55. Imazio M, Cecchi E, Correndo L, Antonielli D'Oulx E, Doronzo B, Trinchero R. Treatment of refractory recurrent pericarditis. Case report and review. *J Cardiovasc Med* 2007;**8**:748–753.
56. Imazio M, Brucato A, Adler Y, Brambilla G, Artom G, Cecchi E, Calmieri G, Trinchero R. Prognosis of idiopathic recurrent pericarditis as determined from previously published reports. *Am J Cardiol* 2007;**100**:1026–1028.